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Long-Term Prognostic Importance of Diabetes After a Myocardial Infarction Depends on Left Ventricular Systolic Function

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OBJECTIVE—This study was performed to understand how left ventricular function modulates the prognostic importance of diabetes after myocardial infarction (MI).

RESEARCH DESIGN AND METHODS—Consecutively hospitalized MI patients screened for three clinical trials were followed for a median of 7 years. Multivariable Cox regression models were used to assess the risk of mortality associated with diabetes, and the importance of diabetes was examined independently within defined left ventricular ejection fraction (LVEF) subgroups.

RESULTS—A total of 16,912 patients were included; 1,819 (11%) had diabetes. Diabetes and 15% unit depression in LVEF were of similar prognostic importance: hazard ratios (HRs) were 1.45 (95% CI 1.37–1.54) and 1.41 (1.37–1.45) for diabetes and LVEF depression, respectively. LVEF modified the outcomes associated with diabetes, with HRs being 1.29 (1.19–1.40) and 1.61 (1.49–1.74) in patients with LVEF <40% and LVEF ≥40%, respectively ($P = 0.03$).

CONCLUSIONS—Patients within the higher LVEF categories have a greater mortality risk attributable to diabetes than patients within the lower LVEF categories.

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Diabetic patients without myocardial infarction (MI) and MI patients without diabetes have a high and equally adverse long-term risk of cardiovascular death compared with the general population (1,2). As well as diabetes, the presence of systolic dysfunction and heart failure are major risk factors for mortality after MI. A recent study suggested that diabetes may be regarded as a risk equivalent to low left ventricular ejection fraction (LVEF) and that ordinary LVEF risk stratification may not be valid in these patients (3). This study was performed to further clarify their interrelationship.

RESEARCH DESIGN AND

METHODS—The current study population comprised Danish patients

consecutively screened for entrance in the Trandolapril Cardiac Evaluation (TRACE) study (4), the Danish Investigations of Arrhythmia and Mortality on Dofetilide Myocardial Infarction (DIAMOND-MI) study (5), and the Bucindolol Evaluation in Acute MI Trial (BEAT) study (6). Full study designs have been described previously (4–6). In brief, departments participating in any of the studies were required to screen consecutive patients admitted with acute MI. All screenings included a transthoracic echocardiogram, which was analyzed in a core laboratory by independent investigators. LVEF was estimated through a global wall motion index, a nine-segment model in the TRACE study (7), and a 16-segment model in the DIAMOND-MI and BEAT studies (8).

This way of obtaining LVEF has a good correlation with outcomes (7).

All comorbidities including the diagnosis of diabetes were by patient history, patient files, and investigator's determination. The outcome analyzed was the risk of all-cause mortality. Survival status was obtained from the National Population Register on 28 May 2008, giving a maximal observational time of 18 years.

Statistical analysis

Continuous variables were compared with a t test and discrete variables with the χ^2 test. Cox proportional hazards models were used for analyses of mortality rates. All models were adjusted for age, sex, LVEF, chronic obstructive pulmonary disease, hypertension, presence of clinical heart failure, a variable indicating the wall motion index scoring system (9 vs. 16 segments), and calendar year of hospitalization. Test for interaction between LVEF and diabetes was done by inclusion of an interaction term in the Cox model with LVEF included as a continuous variable. The relative importance of diabetes was examined independently in patients within defined groups according to LVEF. All analyses were done using SAS version 9.1 (SAS Institute, Cary, NC).

Ethics

All studies were approved by the relevant ethical committees and were conducted in conformity with the Declaration of Helsinki.

RESULTS—A total of 16,912 patients were included in the present analysis. Patients with diabetes were found to be older (69 ± 11 [SD] vs. 67 ± 12 years), have a lower LVEF (41 ± 12 vs. $45 \pm 12\%$), a higher frequency of women (38 vs. 30%), a higher prevalence of clinical heart failure (62 vs. 44%), lower creatinine clearance (69 ± 1 vs. 72 ± 1 mL/min/1.73 m²), and higher BMI (26.9 ± 0.1 vs. 25.9 ± 0.1 kg/m²) than patients without diabetes.

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During a median observational time of 2,609 days (interquartile range 820–3,937), 1,396 (77%) patients with diabetes and 8,985 (60%) patients without diabetes died, respectively. Figure 1 presents the unadjusted mortality rates for some given intervals of LVEF in patients with and without diabetes. Decreasing LVEF subgroup was associated with increasing hazard ratios (HRs) (adjusted for age, sex, wall motion index analysis method, and calendar year): 1.02 (0.81–1.27), 1.46 (1.34–1.60), 1.84 (1.64–2.06), and 1.61 (1.44–1.80) in the LVEF <25%, LVEF 25–35%, LVEF 36–50%, and LVEF >50% subgroups, respectively. In multivariable Cox analysis, diabetes and a 15% unit depression in LVEF were found to be of similar prognostic importance: HRs 1.45 (95% CI 1.37–1.54) and 1.41 (1.37–1.45) for diabetes and LVEF depression, respectively. The prognostic importance of diabetes was modulated by LVEF; *P* for interaction between diabetes and LVEF = 0.03. Among patients with low LVEF (<40%), diabetes

was associated with HR 1.29 (1.19–1.40), which corresponded to the importance of having 10% unit depression in LVEF (HR 1.26 [1.24–1.28] in the overall analysis). Among patients with a high LVEF ($\geq 40\%$), diabetes was associated with HR of 1.61 (1.49–1.74) and was of similar prognostic importance as 20% unit depression in LVEF (HR 1.58 [1.53–1.64]).

CONCLUSIONS—This study demonstrated that the prognostic importance of diabetes depends on left ventricular function, with diabetes having a stronger negative influence with preserved ventricular function. This result was also found in another study (3) and may appear counterintuitive given the detrimental influence of diabetes in patients with heart failure (9). However, the relationship between diabetes and heart failure is bidirectional, and diabetes may not always contribute causally to the adverse prognosis. For example, it is known that a great proportion of patients with severe heart failure will develop diabetes over time (10).

Other studies have in accordance with our finding reported the risk of dying from diabetes after MI to be greatest among patients with lowest baseline mortality risk (11) and among patients with mildest coronary artery lesions (12). In our study, diabetes was associated with a 60% increase in relative risk of mortality among patients with preserved LVEF. Although in the current study it was impossible to investigate what exactly may have driven this increase in risk, complications such as incident heart failure are common over time and are associated with a poor prognosis (13,14).

Finally, as previously reported (3), the protective effect on mortality associated with good left ventricular function after MI was found to be attenuated by diabetes, with diabetes conferring a risk equivalent to 10–20% unit depression in LVEF. With regards to prognostic stratification, this is clinically important because predischARGE assessment of LVEF should be interpreted differently in patients with diabetes.

Limitations

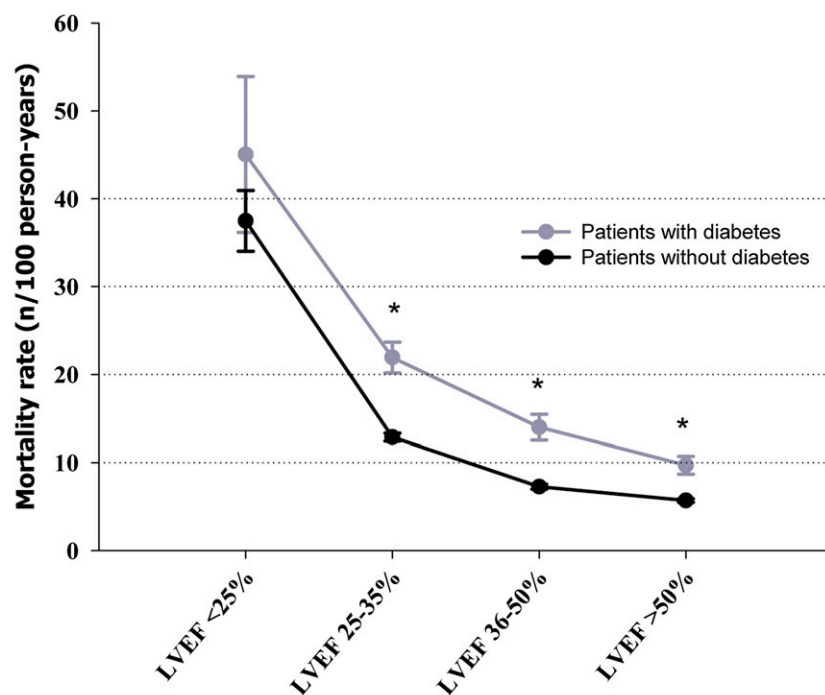
The diagnosis of diabetes relied on patient history, and oral glucose tolerance tests were not performed on a routine basis. LVEF was estimated by wall motion index, which is observer-dependent and an approximation of LVEF. The current study did not have information on diabetes duration, HbA_{1c} values, incident diabetes, use of glucose-lowering agents, or diastolic function, which may have influenced outcomes. Finally, the subgroup of patients with LVEF <25% was small; therefore, a small true increase in HR associated with diabetes cannot be excluded.

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C.A. wrote the initial draft of the manuscript and participated in data analysis. Study design came from S.D.S., C.T.-P., and L.K., who also analyzed data. All authors contributed equally to discussion and critical review of the manuscript.

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Numbers events / total:				
Diabetes	99/103	596/689	350/476	351/551
No diabetes	451/478	3152/4240	2425/4312	2957/6063

Figure 1—Mortality rates per 100 person-years according to LVEF in patients with and without diabetes. Error bars represent 95% CIs. **P* < 0.0001 for differences between patients with and without diabetes (obtained from unadjusted Cox analyses); LVEF <25% subgroup *P* for difference = 0.6.

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